

Perioperative Intravenous
Lidocaine Infusion for Patients
Undergoing Laparoscopic and
Open Pancreatectomies

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Research Protocol Submission Template

Title of the study: Perioperative Intravenous Lidocaine Infusion for Patients Undergoing Laparoscopic and Open Pancreatectomies

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Abstract

DESCRIPTION:

Patients undergoing major intra-abdominal surgeries, such as pancreatectomies, face the challenge of postoperative pain control, return of bowel function, and postoperative ileus. Epidural analgesia offers benefits in these areas; however, it is utilized rarely at our institution, because it is an invasive procedure with risks and potential complications.

Several studies have demonstrated improved patient rehabilitation after abdominal surgery in which patients received perioperative intravenous (IV) infusion of lidocaine. As an adjunct to multimodal analgesia, IV lidocaine infusion in colectomy patients has been shown to decrease postoperative pain, opioid consumption, postoperative ileus, and length of hospital stay. The purpose of this study is to evaluate if an IV lidocaine infusion will provide clinical benefits to pancreatectomy patients with regard to analgesia and return of bowel function.

Different titrations of the IV lidocaine infusion for postoperative analgesia have been reported without side effects of local anesthetic toxicity (8).

Research Plan

1. Specific Aims

The objective of this study is to see if perioperative IV lidocaine infusion improves postoperative analgesia and return to bowel function in patients undergoing open and laparoscopic pancreatectomies. If analgesia is improved and return of bowel function is expedited in this patient population, then a standardization of practice will be implemented to improve patient outcomes and reduce hospital length of stay.

2. Background and Significance

The analgesic properties of local anesthetics have been well documented in the literature (1, 2). Proposed mechanism for systemic analgesia include antinociceptive effects by blocking sodium and potassium channels, pain modulation in the CNS by inhibiting NMDA and NK receptors, and antiinflammatory properties (17). Intravenous infusions of lidocaine have been used in several types of surgeries, including orthopedic, breast, abdominal, and gynecological surgeries. Intra-abdominal surgeries involving bowel resection have shown the most favorable outcomes in improved analgesia and improved rate of return of bowel function (3, 4, 5). Significant evidence also demonstrates that epidural analgesia helps with pain control and return of bowel function in patients undergoing a variety of open and laparoscopic intraabdominal cases (6, 7). However, routine use of epidural analgesia is implemented infrequently due to an epidural being an invasive procedure with its own associated risks and complications. Based on this known information, an intravenous lidocaine infusion protocol is being proposed to assess post-operative pain control and improved return to bowel function in patients undergoing open and laparoscopic pancreatectomies.

3. Progress Report and Preliminary Studies

Lidocaine infusion during pancreatic surgery, to date, has not been studied. A few trials in cooperation with Dr. Asbun have taken place, since January 2015., the patients demonstrated subjectively improved pain control in the recovery room and decreased opioid consumption. Plasma lidocaine levels measured in 8 patients averaged 2.26 ug/ml (range 1.2 – 3.3 ug/ml), and they were consistently below toxic levels and no side effects were noted nor reported by the patient.

4. Research Design and Methods

Study Design or Overview –

50 patients will be recruited in the study. Prior to the day of surgery, all patients are seen by their surgeon for their pre-surgical evaluation. At the time, the patient will be consented to participate in the study involving lidocaine infusion to improve post-operative pain and control and return of bowel function.

As is current practice at our institution for intra-abdominal cases including pancreatectomy surgery, an ***Enhanced Recovery Pathway (ERP)*** will be utilized as outlined below:

Pre-operative multimodal non-opioid analgesics (single dose P.O. with water):

- Celecoxib 400 mg
- Gabapentin 600 mg
- Acetaminophen 1000 mg

Intraoperative management:

- Maintenance of general anesthesia will be standardized to sevoflurane with air/oxygen mixture at 2 L/min

- Fentanyl will be the only opioid use at induction of anesthesia and during the surgery.
- Fluid administration goals – (modified as clinical circumstances dictate)
 - 500 mL per hour for laparoscopic cases
 - 800 mL per hour for open cases
 - Phenylephrine or ephedrine boluses as needed to maintain mean arterial pressure (MAP) > 60 mmHg
- Postoperative nausea and vomiting (PONV) prophylaxis
 - Dexamethasone 4 mg I.V. at anesthesia induction (one dose)
 - Ondansetron 4 mg I.V. 30 minutes before emergence from anesthesia (one dose)
 - For patients with a history of PONV, droperidol 0.625 mg I.V. or promethazine 12.5 mg I.V. will be given as a third anti-emetic agent.
- Nasogastric (NG) or Orogastric (OG) tube is to be removed at the end of the case unless specified by the surgical team.

Postoperative non-opioid analgesics:

- Acetaminophen 1000 mg PO every 6 hours
- Ketorolac 30 mg IV every 6 hours to start after the surgery (total of 4 doses)
 - For patients >65 years old or <50 kg use 15 mg of ketorolac IV
- Ibuprofen 800 mg PO every 6 hours after the last ketorolac dose
 - For patients >65 years old or <50 kg use 400 mg of ibuprofen PO

Opioid analgesia

- Patient Controlled Analgesia (PCA) with IV hydromorphone will be utilized in the first 24 hours
- IV or PO hydromorphone will be used for breakthrough pain

Diet:

- Soft, low residue diet evening of POD #0
- Advance to low fat diet excluding raw vegetables and fresh fruit at 0700 on postoperative day 1 if patient without nausea.
- If patient is diabetic, advance to diabetic diet excluding raw vegetables and fresh fruit at 0700 on postoperative day 1 if patient without nausea.

Activity:

- Out of bed greater than 1 hour, including 1 or more walks and sitting in chair within 2 hours of reaching the surgical floor
- Day after surgery and until discharge, out of bed greater than 6 hours, including 4 or more walks and sitting in chair
- All meals out of bed

Intraoperative lidocaine infusion protocol

On the day of surgery, the patient will be randomly assigned to either the lidocaine infusion (2 grams of lidocaine in 500cc D5W) study group (n=25 patients) or the control group (n=25 patients) who will receive 500cc of D5W infusion with no lidocaine. Pharmacy will handle randomization of patients. The patient, the surgeon, the anesthesiologist and the postoperative

nursing staff will be blinded to which group patients were assigned. The infusion bag will be dispensed by pharmacy based on the randomization protocol and labeled “Lidocaine Infusion Study” with the corresponding IRB number.

The anesthesiologists assigned to the case will begin with a bolus infusion of lidocaine, 1.5 mg/kg (max 100 mg of lidocaine) at the time of anesthesia induction, followed by a continuous infusion set at 1.5 mg/kg/hour from the IV bag labeled “Lidocaine Infusion Study”

Actual body weight will be utilized in the dosing of lidocaine with a limit of 100mg of lidocaine bolused and maximum infusion rate not to exceed 3mg/min. Patients with BMI >40 are excluded from the study.

Intraoperative opioids will be limited to fentanyl in order to standardize intraoperative opioid requirements and intraoperative ketamine will be avoided. The surgical team is instructed not to infiltrate the surgical wound with local anesthetic during or at the end of surgery. The lidocaine infusion will be continued in the PACU. The nurse in the PACU will be instructed to discontinue the infusion when the patient meets PACU discharge criteria. The nurse and the surgical team are instructed not to use fentanyl during the postoperative period for analgesia. Prior to the discontinuation of the infusion, every patient will have a lidocaine level drawn before leaving the PACU.

Intra-op and PACU *stopping* rules

- If unstable arrhythmias are noted in the OR/PACU, the infusion will be stopped and a plasma lidocaine level will be drawn.
- If symptomatic bradycardia and significant hypotension refractory to treatment, consider stopping the infusion.
- If significant intra-operative hemorrhage (1 body blood volume), consider stopping the infusion.
- If the patient requires ICU admission after surgery due to intraoperative complications, the infusion will be stopped at the end of surgery.
- If the patient in the PACU demonstrates sudden changes in mental status, convulsion, or coma, the infusion will be stopped and a lidocaine level will be drawn.
- If mortality or major complications were to occur during the study, the cases will be reviewed by the primary investigator and co-investigators to determine the cause and if poor outcome is related to the study. All such cases will also be reported to IRB.

Baseline Assessments

1. Pain at rest and with coughing via a Numerical Rating Scale (NRS) – completed on the day of surgery in preop holding area
2. Quality of Recovery (QoR-15) questionnaire – completed at the time of consenting or preop on the day of surgery.

Assessment and management in the PACU (day of surgery)

1. Pain scores via a Numerical Rating Scale (NRS) will be assessed in the PACU at rest and with coughing at the time of PACU arrival and at 30 minute intervals (Appendix A). (15) If the

patient is too somnolent upon arrival in the PACU and unable to participate, then the findings are to be documented as such (i.e., unable to participate).

2. Upon arrival to PACU and at 30 minutes, patient's level of consciousness will be assessed via the Richmond Agitation-Sedation Scale (RASS) (Appendix B).
3. Upon arrival to PACU and at 30 minute intervals the patient will also be evaluated by the PONV Impact Score (Appendix C).
4. Fentanyl use will be avoided in the PACU.
5. Total opioid requirements in the PACU will be noted. Converted to morphine equivalents as per Table 1.
6. Use of ketorolac or acetaminophen will be noted
7. Incidence of nausea/vomiting and administered treatment in PACU will be noted.
8. PACU length of stay (defined as the time from PACU admission until discharge criteria are met as per PACU nurse evaluation and documentation).
9. At time of the patient meeting discharge criteria in the PACU, lidocaine infusion will be stopped and lidocaine plasma levels will be drawn in all patients in order to keep the PACU staff blinded.

Assessment of the patient on the floor

1. The patient will be assessed by floor nurse on POD #0 at 8 PM and POD #1 at 8 AM and 8PM.
2. Pain will be assessed via the NRS scale at the prescribed times at rest and with coughing. Nurses will also rate the patients' average pain on a scale from 0 to 10 (0=no pain; 10=worst pain ever experienced) in the past 12 hours, or since their time of surgery if it is POD #0.
3. The current level of consciousness will be evaluated using the RASS score.
4. At 24 hours from the time of arrival to PACU, the patient's quality of recovery will be evaluated by the one of the study coordinators via a validated 15-question Quality of Recovery (QoR – 15) questionnaire.
5. At 24 hours from the time of arrival to PACU, the score on PONV Impact Scale will be obtained.
6. Need for nasogastric (NG) tube during hospital stay will be noted.

Return of bowel function

During the patients hospital stay, the time to first flatus and first bowel movement will be noted as per progress note of the surgical team. The surgical team is specifically instructed to ascertain these recovery milestones every morning during clinical rounds.

Additional data include

1. Duration of surgery (in minutes)
2. Time when PACU discharge criteria are met (in minutes)
3. Length of hospital stay
4. QoR-15 questionnaire via telephone call 2 to 3 weeks from the day of surgery.

b. Study Subjects.

Inclusion criteria:

- All adult patients undergoing elective open or laparoscopic total pancreatectomies and pancreatoduodenectomies (i.e., Whipple procedure), and participating in the ERP.
- Age 18 – 80 years old
- ASA class I – III
- BMI < 40
- Ability to understand and read English

Exclusion criteria:

- Not able or willing to sign consent
- Intolerance or allergy to opioids, NSAIDS, acetaminophen, or amide-type local anesthetics (i.e., lidocaine).
- History of epilepsy or currently receiving treatment for seizures
- Severe hepatic insufficiency (Child-Pugh Score C) – if documented in patient's medical history
- Renal insufficiency (creatinine clearance less than 30 mL/minute) – if documented in patient's medical history
- Advance heart failure
 - NY Heart failure stage 3 or greater
 - Ejection function <30%
- Cardiac arrhythmias:
 - 2nd and 3rd degree heart block, sick sinus syndrome, symptomatic bradyarrhythmias, Wolff-Parkinson-White (WPW) syndrome, or Stokes-Adams syndrome
 - Left bundle branch block or bifascicular block
 - *Not to exclude* patients the following conditions unless clinical circumstance dictate:
 - Atrial fibrillation or atrial flutter
 - Presence of Implantable Cardioverter Defibrillator (ICD), or pacemakers
- Patients on anti-arrhythmic therapy (i.e., digoxin, amiodarone, flecainide, lidocaine, sotalol, etc.)
 - *Not to exclude* patients on beta blockers (i.e., metoprolol, atenolol, etc.) unless clinical circumstance dictate
- Patients with active psychiatric disorders (such as schizophrenia, bipolar disorder) or cognitive dysfunction
- Pregnancy or lactating
- Enucleation, central, and distal pancreatectomy
- Opioid tolerance (defined as consumption of greater than 30 mg of oxycodone per day)

Sample Size – The study will include 50 patients to be randomized and blinded in two groups of 25 patients each. No prior studies have been conducted on patients undergoing pancreatectomies and receiving a lidocaine infusion. However, several studies have shown statistical significant improvement in postoperative pain control and reduction of opioid requirement with the use of lidocaine infusion for intraabdominal surgeries, and often requiring 20 to 50 patients. (8) Additional 7 subjects will be screened to reach target accrual of 50 patients.

Data Collection –

Preoperative

1. Age, Sex, ASA Physical Status, Height, Weight, and BMI
2. Analgesics including opioids, NSAIDs, and/or acetaminophen (as per home medication list)
3. Current pain score as per NRS scale
4. QoR - 15

Intraoperative

1. Total pancreatectomies or pancreatoduodenectomies (as per post-op surgical note)
2. Open or laparoscopic (note if the case was converted to open)
3. Surgeon 1 or 2 (Drs. Asbun or Stauffer)
4. Duration of surgery
5. Duration of lidocaine infusion (time from induction to discontinuation in the PACU)
6. Total amount of fentanyl used in the OR.
7. Amount of anesthetic gas used (sevoflurane at 2L/min of fresh gas flow)
 - i. At the conclusion of the surgery, the anesthetic gas consumption will be as recorded by our Apollo Anesthesia Machine – Dräger
 - ii. Hourly vapor anesthetic requirements will be determined by the total anesthetic gas used divided by duration of the case (intubation time to surgery end time)

PACU

1. Pain score on arrival to PACU and at 30 minutes at rest and with coughing using the NRS scale
2. RASS score on arrival to PACU and 30 minutes after PACU admission
3. Incidence of PONV as reported and treated by PACU nurse.
4. Opioid requirements as converted into morphine equivalents (Table 1)
5. Use of acetaminophen or NSAIDs
6. Total PACU time (arrival to PACU until meeting discharge criteria as per PACU nurse)
7. Time of the discontinuation of the infusion
8. Plasma lidocaine level at the discontinuation of the infusion

Table 1: Morphine-equivalent based on an opioid equianalgesic

Opioid Drug (mg)	Administered	equianalgesic ratio to oral morphine
Morphine	PO	1:1
Morphine	IV	3:1
Oxycodone	PO	1.5:1
Hydrocodone	PO	1:1
Fentanyl	IV	300:1
Fentanyl	Transdermal	70:1
Oxymorphone	PO	3:1
Oxymorphone	IV	30:1
Hydromorphone	IV	18:1
Hydromorphone	PO	4:1
Tramadol	PO	0.3:1

Postoperative day 0 -1

1. POD #0 at 8PM and POD #1 at 8AM and 8PM:
 - a. Current pain via NRS scale at rest, coughing, and average of the past 12 hours or since surgery if POD #1
 - b. Current RASS score
2. At 24 hours from arrival to PACU
 - a. Quality of Recovery (QoR – 15) questionnaire with assistance of a co-investigator (16).
 - b. Opioid requirements as converted into morphine equivalents
 - c. Acetaminophen or NSAIDs use

Hospital stay

1. First time to flatus (in days)
2. First time to bowel movement (in days)
3. Presence of NG tube (in days)
4. Length of hospital stay (in days)

Outpatient follow up

1. QoR – 15 via telephone call

Data Handling – Data will be entered into a secure REDCap database by study assistant. Principal Investigator will verify data to ensure accuracy.

Data Analysis - A t-test will be used to analyze mean differences in NRS scores, opioids requirements, and return of bowel function between groups. Complication rates will be analyzed using a Chi-squared analysis.

Feasibility and Time Frame – About 100 pancreatectomies per year are done at our institution. Anticipating that 50% of patients are not enrolled due to the exclusion criteria or unwillingness to

participate in the study, the anticipated time frame of patient recruitment for this study will be one year.

Strengths – The study focuses on a patient population that frequently has difficulties with postoperative pain control, delayed return of bowel function and ileus, which are often exacerbated by opioids. This study will determine if incorporating lidocaine infusions will be of help to this patient population. Also, the proposed study has been previously performed on similar surgical procedures with demonstrating improved postoperative analgesia and without any adverse outcomes (8, 9, 10). All drugs and personnel required for this study are readily available and in place at Mayo Clinic.

Limitations – Even though highly unlikely, the potential for local anesthetic toxicity exists. During the patients' intraoperative course, EKG, blood pressure, and pulse oximeter will be closely monitored for any potential signs of arrhythmias. If there is any suspicion of local anesthetic toxicity, the infusion will immediately be discontinued, the anesthesiologist taking care of the patient will be unblinded, and a serum level of lidocaine will be drawn at that time if appropriate. Close monitoring of the patients will also continue to take place in the PACU, as is the standard of care.

5. Human Subjects

Detailed Description: All human subjects will meet the criteria aforementioned and will be undergoing open or laparoscopic total and subtotal pancreatectomies.

Population: Patients who are scheduled to undergo either open or laparoscopic pancreatectomy will be given the opportunity to provide an informed consent for this study. Patients will be selected without regard to race or gender. We plan to enroll 50 patients who will meet inclusion and exclusion criteria.

Research Materials: Data elements will be obtained from the patients' medical record and entered into REDCap database

Recruitment of Subjects: Patients will be recruited at the surgeon's office, during their pre-operative visit. The prospective candidates for the study will be approached by the study team member. Patients will be given information regarding the drug, the potential benefits, and complications of being enrolled in the study. Patients will be given adequate time to review the consent form, ask questions, and make an informed decision to either participate or decline.

Potential Risks: Even though highly unlikely, the potential for unknown local anesthetic toxicity exists. Early or mild sign and symptoms of toxicity include sudden dizziness, confusion, tinnitus, metallic taste, and numbness or tingling of fingers, toes, or lips. These signs and symptoms may progress to convulsions, unconsciousness, sudden hemodynamic instability, cardiac arrhythmias, or cardiac arrest. To date, there are no documented cases of morbidity or mortality associated with IV lidocaine analgesia.

Every participant in this study will be closely monitored by the anesthesia providers. During their intraoperative course and in the PACU, EKG, blood pressure and pulse oximeter will be closely monitored for any potential signs of arrhythmias. If there is any suspicion of local anesthetic toxicity, then the infusion will immediately be discontinued and a serum level of lidocaine will be drawn at that time. The study team members will become unblinded to determine the relatedness of side effects to the study drug.

Protection: The patient will be enrolled into a randomization table and a number will be assigned to them. The randomization assignments will be handled through REDCap database by a research pharmacist. Only study team members will have access to this project in the database. All study-related regulatory documents will be stored electronically on the Department of Anesthesia research drive. The access to this research folder is limited to study team members and information backed up by Mayo Clinic's IT department to secured servers.

Benefits: Patients undergoing pancreatectomies often have decreased bowel function, difficult to control post-operative pain, and prolonged hospital stays. The study focuses to reduce these factors and improve patient outcome. The potential risks are minimal to none. Numerous previous studies have not demonstrated adverse outcomes to the patients.

6. Gender/Minority Mix

We plan to enroll the 50 patients regardless of race or gender. The exclusion will be made as previously described in Research Design and Methods section. Women of childbearing potential will be included in this study provided that they had a negative pregnancy test performed as part of their routine preoperative work-up.

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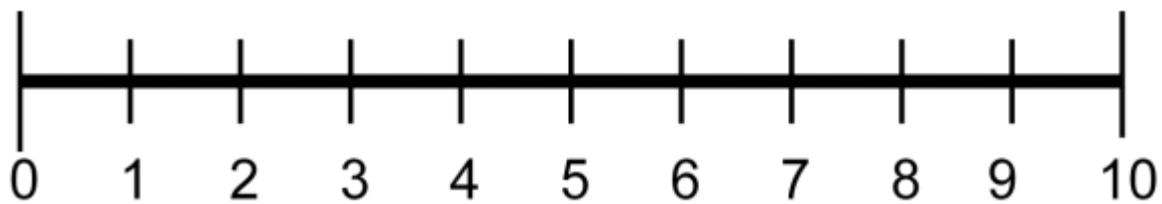
8. Other:

Budget: The proposed budget will include the costs associated with:

- 1) Laboratory tests for plasma lidocaine levels (one per each enrolled subject)
 $\$17.50 \times 50 = \875
- 2) Lidocaine infusion bags (2g/500cc D5W) for 25 patients
 $\$8.55 + \$1.90 + \$55 = \$65.45 \times 25 = \$1636.25$
- 3) 500 cc D5W infusion bag
 $\$6.73 + \$1.90 + \$55 = \$63.63 \times 25 = \$1590.75$
- 4) Initial pharmacy fee (one time)
 $\$1700$
- 5) Total budget for one year: \$5,802
- 6) **Total budget including 30% indirect rate: \$7,542.60**

9. Appendix

Appendix A – Pain Assessed via the Numerical Rating Scale (NRS) (11)



The patient is asked to rate their current pain on a scale from 0 (no pain) to 10 (worst pain imaginable) at rest and with coughing.

Appendix B – Richmond Agitation-Sedation Scale (12)

Score	Classification	Description
4	Combative	Overly combative, violent, immediate danger to staff
3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
2	Agitated	Frequent nonpurposeful movements; fights ventilator
1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening/eye contact >10 seconds)
-2	Light Sedation	Briefly awakens with eye contact to voice (< 10 seconds)
-3	Moderate Sedation	Movement or eye opening to voice but no eye contact
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Appendix C – The PONV Impact Scale (13)

Q1. Have you vomited or had dry-retching*?

- 0. No
- 1. Once
- 2. Twice
- 3. Three or more times

Q2. Have you experienced a feeling of nausea ("an *unsettled feeling in the stomach and slight urge to vomit*")? If yes, has your feeling of nausea interfered with activities of daily living, such as being able to get out of bed, being able to move about freely in bed, being able to walk normally, or eating and drinking?

- 0. Not at all
- 1. Sometimes
- 2. Often or most of the time
- 3. All of the time.

To calculate the PONV Impact Scale score, add the numerical responses to questions 1 and 2. A PONV Impact Scale score of ≥ 5 defines clinically important PONV.

**count distinct episodes: several vomits or retching events occurring over a short time frame, say 5 min, should be counted as one vomiting/dry-retching episode; multiple episodes require distinct time periods without vomiting/dry-retching.*

Appendix D – Quality of Recovery (QoR – 15) Questionnaire (14)

QoR-15 Patient Survey

Date: ___/___/___

Study #: _____

Preoperative

Postoperative

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2. Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3. Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4. Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5. Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6. Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7. Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8. Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9. Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10. Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12. Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13. Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14. Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15. Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time